NATIONAL MARROW DONOR PROGRAM®

Entrusted to operate the C.W. Bill Young Cell Transplantation Program,
including Be The Match Registry®

October 31, 2011

CDR Sheri Parker
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: **Quarterly Performance/Technical Report of the National Marrow Donor Program®**

Reference: Grant Award #N00014-10-1-0204 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Parker:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of July 1, 2011 to September 30, 2011.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis L Confer, MD directly at 612-362-3425.

With this submittal of the quarterly progress report, the National Marrow Donor Program has satisfied the reporting requirements of the above reference for quarterly documentation. Other such quarterly documentation has been previously submitted under separate cover.

Please direct any questions pertaining to the cooperative agreement to my attention at 612-362-3403 or at cabler@nmdp.org.

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Sr. Contracts Representative

Enclosure: Quarterly Report with SF298

C: D. Ivery – ACO (ONR-Chicago)
Dr. Robert J. Hartzman, CAPT, MC, USN (Ret)
Jennifer Ng, PhD – C.W. Bill Young Marrow Donor Recruitment and Research Program
J. Rike - DTIC (Ste 0944)
NRL (Code 5227)
Dennis Confer, MD, Chief Medical Officer, NMDP
Stephen Spellman

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Spellman, Stephen

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3001 Broadway St., N.E., Ste. 500
Minneapolis, MN 55413

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Arlington, VA 22203

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14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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U	U	U			19b. TELEPONE NUMBER (*Include area code)* 612.362.3425

NATIONAL MARROW DONOR PROGRAM®

Creating Connections. Saving Lives.™

Grant Award N00014-10-1-0204

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

QUARTERLY PERFORMANCE / TECHNICAL REPORT

FOR

JULY 01, 2011 to SEPTEMBER 30, 2011

PERIOD 6

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
1-800-526-7809

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IIA. Contingency Preparedness – Objective 1: Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians	
IIA.1 Task 1: Secure Interest of Transplant Physicians	**Period 6 Activity:** • Held Advanced Medical Radiation Response training at the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oakridge, TN for 23 RITN center staff, including eight (8) physicians
IIA.1 Task 2: GCSF in Radiation Exposure	**Period 6 Activity:** • No activity during this reporting period
IIA.1 Task 3: Patient Assessment Guidelines and System Enhancements	**Period 6 Activity:** • No activity during this reporting period
IIA 1 Task 4: National Data Collection Model – This task is closed.	
IIA. Contingency Preparedness – Objective 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
IIA.2 Task 1: Contingency Response Network	**Period 6 Activity:** • The web based learning management system (LMS) vendor SumTotal has been selected to implement the future training portal. o Implementation will begin in November with a planned Phase I launch scheduled for March 1, 2012. • Continued to maintain and test the Iridium satellite telephones issued to RITN centers
IIA.2.2 Task 2: Sibling Typing Standard Operating Procedures	**Period 6 Activity:** • No activity during this reporting period

IIA. Contingency Preparedness – Objective 3: NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.	
IIA.3 Task 1: I.S. Disaster Recovery	**Period 6 Activity:** • No activity during this reporting period
IIA.3 Task 2: Critical Facility and Staff Related Functions	**Period 6 Activity:** • Verified configuration of and then secured all business continuity equipment at the data center; this equipment will ensure key staff can access NMDP systems from up to ten remote non-NMDP locations.
IIB. Rapid Identification of Matched Donors – Objective 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.	
IIB.1 Task 1: Increase Registry Diversity	**Period 6 Activity:** • During this past quarter, as an ongoing project of reviewing rare alleles reported on donors in the Be The Match Registry, 139 donors with rare alleles were identified and retyped. To date, 1150 samples have been sent to a contract laboratory for high resolution typing at A, B, C, or DRB1. In total, 903 (60%) donor typings have changed from the previously reported rare allele and 605 donor typings have been confirmed to carry the reported rare allele.
IIB.1 Task 2: Evaluate HLA-DRB1 High Res typing – This task is closed.	
IIB.1 Task 3: Evaluate HLA-C Typing of Donors – This task is closed.	
IIB.1 Task 4: Evaluate Buccal Swabs	**Period 6 Activity:** • No activity during this reporting period
IIB 1 Task 5: Enhancing HLA Data for Selected Donors	**Period 6 Activity:** The AB only donor DRB1 typing project initiated last quarter continued. AB only repository samples identified from daily queries of NMDP preliminary patients with no 6/6 A/B/DRB1 potential allele matches.

	Results to date: • Through 9/28/11 a total of 2,976 samples, corresponding to 180 patient searches, were tested for DRB1. • Two DRB1 allele matched donors were identified • One of the DRB1 matches was selected for stem cell donation, a full 10/10 match for a patient with no previous 6/6 potentials • The second DRB1 match subsequently mismatched the project patient at both the A and C locus • An abstract was submitted for consideration at ASBMT 2012 Tandem meeting.
IIB 1 Task 6: Maintain a Quality Control Program – This task is closed.	
IIB. Rapid Identification of Matched Donors – Objective 2: Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.	
IIB 2 Task 1: Collection of Primary Data	**Period 6 Activity:** • No activity during this reporting period
IIB 2 Task 2: Validation of Logic of Primary Data – This task is closed.	
IIB 2 Task 3: Reinterpretation of Primary Data – This task is closed.	
IIB 2 Task 4: Genotype Lists & Matching Algorithm	**Period 6 Activity:** • No activity during this reporting period

IIB. Rapid Identification of Matched Donors – Objective 3: Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor.	
IIB.3 Task 1: Phase I of EM Haplotype Logic	**Period 6 Activity:** The following enhancements to the HapLogic algorithm were completed during this reporting period: • Established a HapLogic 3 baseline for on-going testing. • Identified and corrected multiple problems with the matcher code which computes the match percentages between a single recipient and donor. This resulted in steady improvement in the predictive performance of the HapLogic 3 algorithm. • Changed multiple components of the system architecture including the database and user interface to accommodate new information such as x/8 and x/10 match percentages. • Revised and enhanced the HapLogic-tools user interface, which was specifically developed for users of HapLogic 3. • Completed multiple rounds of algorithm validation using various sets of preliminary 6-locus haplotype frequency data.
IIB 3 Task 2: Enhancement of EM Algorithm	**Period 6 Activity:** • Calculated 6-locus A~C~B~DRB3/4/5~DRB1~DQB1 haplotype frequencies on 21 detailed race populations and 5 rollup race populations using Blocks/Imputation EM approach on the entire DNA-typed registry. • Tested 6-locus haplotype frequencies in a development version of the HapLogic III matching algorithm and found significant improvements in predictions of allele matching compared to the production Maiers 2007 haplotype frequency dataset.
IIB 3 Task 3: Optimal Registry Size Analysis	**Period 6 Activity:** • Revised and submitted Math Model manuscript to the journal Tissue Antigens. • Developed draft of Registry Models Physician-Oriented manuscript in collaboration with Dr. Mary Eapen of CIBMTR.

IIB 3 Task 4: Target Under- Repre-sented Phenotypes	**Period 6 Activity:** • No activity during this reporting period
IIB 3 Task 5: Bioinformatics Web Site – This task is closed.	
IIB 3 Task 6: Consultants to Improve Algorithm – This task is closed.	
IIB 3 Task 7: Population Genetics – This task is closed.	
IIB 3 Task 8: Haplotype Matching – This task is closed.	
IIB 3 Task 9: Global Haplotype/Benchmark – This task is closed.	
IIB. Rapid Identification of Matched Donors – Objective 4: Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.	
IIB.4 Task 1: Expand Network Communications	**Period 6 Activity:** • No activity during this reporting period
IIB.4 Task 2: Central Contingency Management	**Period 6 Activity:** Donor testing continued for the research project to validate the "actual" HLA-A, B, C and DRB1 (8/8) high resolution match rates for CAU, AFA, HIS, and API patients. Testing was done on new samples from swab kits sent to donors that had no remaining stored repository samples. In this period 150 swab kits were sent to donors who had confirmed current addresses. Testing was performed on 77 loci for 74 donors that returned the kits during the reporting period and results compiled for the analysis. Analysis for 8/8 high resolution matches is nearing completion. Analysis for 10/10 high resolution matches (adding DQB1) on patients where an 8/8 match was identified was initiated. Additional DQB1 typing was initiated on over 100 donor samples previously typed and stored at the HLA lab.
IIB.4 Task 3: Benchmarking Analysis – This task is closed.	

IIB.4 Task 4: Expand Capabilities of Collection and Apheresis Centers – This task is closed.	
IIC. Immunogenetic Studies – Objective 1: HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found.	
IIC.1 Task 1: Donor Recipient Pair Project	**Period 6 Activity:** Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the Antigen Binding Domain (ABD). This recommendation is based on the hypothesis that amino acid differences outside the ABD are not immunogenic. The ABD allo-reactivity assessment project will give insight into the allowable percent tolerance of matching needed outside of the ABD. • Initiated investigation of the first class II non-ABD mismatch (DRB1*140101/1454) where both alleles have been seen in the same genotype. Specific queries of the Be The Match Registry allowed for selection of ninety-nine potential donors to be typed at high resolution. • 72 donors were invited to participate in the study. 21 study participants consented and submitted blood samples. • Testing was completed on eleven samples of four different haplotype pairs with a testing period of performance from May 9, 2011 to August 31, 2011. • Data analysis has begun and will be completed in the next quarter.
IIC. Immunogenetic Studies – Objective 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2 Task 1: Analysis of non-HLA loci	**Period 6 Activity:** In 2005 a pilot study to perform high resolution KIR gene typing was launched. The primary objectives of the study were to move technology forward from the current practice of locus level typing to high resolution typing, disseminate information and protocols in an open source mechanism and develop reference lines for use in individual laboratories. • 46 novel alleles were fully characterized, submitted and names received. Publication of the new IPD database containing these alleles is expected within the next year.

	• Preparation continued on the KIR Typing Project manuscript. • One abstract was accepted and will be presented at the 2011 American Society of Human Genetics in October 2011.
IIC 2 Task 2: Related Pairs Research Repository – This task is closed.	
IIC 2 Task 3: CIBMTR Integration – This task is closed.	
IID. Clinical Research in Transplantation – Objective 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1 Task 1: Observational Research, Clinical Trials and NIH Transplant Center	**Period 6 Activity:** **Observational Research** • Staff continued work on various observational studies within the area of Immunobiology, GVHD and Graft Sources Working Committees. Staff prepared abstracts for submission to the 2011 American Society of Hemotology (ASH). **Prospective Studies; RCI BMT** • Site monitoring took place during this report period for donor centers participating on the 0201 PBSC vs Marrow clinical trial. Monitors completed 1 visit and monitored records of accrued donors. **Cord Blood Research** • The Duke and St. Louis Cord Blood Bank (SLCBB) discussed training and validating the assay methodologies to ensure consistent results were generated at both testing sites for the study investigating biomarkers associated with cord blood engraftment. o Testing using this third laboratory, SLCBB, is under development to determine whether the poor reliability is due to center-specific or assay related issues. • Contract negotiations with SLCBB were initiated.

IID.1 Task 2: Research with NMDP Donors – This task is closed.	
IID.1 Task 3: Expand Immuno-biology Research	**Period 6 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • Work continued on several draft manuscripts and analyses.

ACRONYM LIST

AABB	American Association of Blood Banks	HR	High Resolution
AFA	African American	HRSA	Health Resources and Services Administration
AGNIS	A Growable Network Information System	HSC	Hematopoietic Stem Cell
AML	Acute Myelogenous Leukemia	IBWC	Immunobiology Working Committee
ABD	Antigen Binding Domain	IDM	Infectious Disease Markers
API	Asian Pacific Islander	IHWG	International Histocompatibility Working Group
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IPR	Immunobiology Project Results
ASBMT	American Society for Blood and Marrow Transplantation	ICRHER	International Consortium for Research on Health Effects of Radiation
ASHI	American Society for Histocompatibility and Immunogenetics	IND	Investigational New Drug
B-LCLs	B-Lymphoblastoid Cell Lines	IS	Information Services
BARDA	Biomedical Advanced Research and Development Authority	IT	Information Technology
BBMT	Biology of Blood and Marrow Transplant	IRB	Institutional Review Board
BCP	Business Continuity Plan	JCAHO	Joint Commission on Accreditation of Healthcare Organizations
BCPeX	Business Continuity Plan Exercise	KIR	Killer Immunoglobulin-like Receptor
BMCC	Bone Marrow Coordinating Center	MDACC	MD Anderson Cancer Center
BMDW	Bone Marrow Donors Worldwide	MDS	Myelodysplastic Syndrome
BMT	Bone Marrow Transplantation	MHC	Major Histocompatibility Complex
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	MICA	MHC Class I-Like Molecule, Chain A
BODI	Business Objects Data Integrator	MICB	MHC Class I-Like Molecule, Chain B
BRT	Basic Radiation Training	MKE	Milwaukee
C&A	Certification and Accreditation	MRD	Minimal Residual Disease
CAU	Caucasian	MSKCC	Memorial Sloan-Kettering Cancer Center
CBMTG	Canadian Blood and Marrow Transplant Group	MSP	Minneapolis
CBB	Cord Blood Bank	MUD	Matched Unrelated Donor

CBC	Congressional Black Caucus	NAC	Nuclear Accident Committee
CBS	Canadian Blood Service	NCBM	National Conference of Black Mayors
CBU	Cord Blood Unit	NCI	National Cancer Institute
CHTC	Certified Hematopoeitic Transplant Coordinator	NEMO	N-locus Expectation-Maximization using Oligonucleotide typing data
CIBMTR	Center for International Blood & Marrow Transplant Research	NHLBI	National Heart Lung and Blood Institute
CIT	CIBMTR Information Technology	NIH	National Institutes of Health
CLIA	Clinical Laboratory Improvement Amendment	NIMS	National Incident Management System
CME	Continuing Medical Education	NK	Natural Killer
CMF	Community Matching Funds	NLE	National Level Exercise
COG	Children's Oncology Group	NMDP	National Marrow Donor Program
CREG	Cross Reactive Groups	NRP	National Response Plan
CSS	Center Support Services	NST	Non-myeloablative Allogeneic Stem Cell Transplantation
CT	Confirmatory Testing	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
CTA	Clinical Trial Application	OIT	Office of Information Technology
DC	Donor Center	OMB	Office of Management and Budget
DHHS-ASPR	Department of Health and Human Service – Assistant Secretary Preparedness and Response	ONR	Office of Naval Research
DIY	Do it yourself	P2P	Peer-to-Peer
DKMS	Deutsche Knochenmarkspenderdatei	PBMC	Peripheral Blood Mononuclear Cells
DMSO	Dimethylsulphoxide	PBSC	Peripheral Blood Stem Cell
DoD	Department of Defense	PCR	Polymerase Chain Reaction
DHHS-ASPR	Department of Health and Human Services – Assistant Secretary for Preparedness and Response	PSA	Public Service Announcement
DNA	Deoxyribonucleic Acid	QC	Quality control
DR	Disaster Recovery	RCC	Renal Cell Carcinoma
D/R	Donor/Recipient	RCI BMT	Resource for Clinical Investigations in Blood and

			Marrow Transplantation
EBMT	European Group for Blood and Marrow Transplantation	REAC/TS	Radiation Emergency Assistance Center/Training Site
EDC	Electronic Data Capture	RFP	Request for Proposal
EFI	European Federation of Immunogenetics	RFQ	Request for Quotation
EM	Expectation Maximization	RG	Recruitment Group
EMDIS	European Marrow Donor Information System	RITN	Radiation Injury Treatment Network
ENS	Emergency Notification System	SBT	Sequence Based Typing
ERSI	Environment Remote Sensing Institute	SCTOD	Stem Cell Therapeutics Outcome Database
FBI	Federal Bureau of Investigation	SG	Sample Group
FDA	Food and Drug Administration	SLW	STAR Link® Web
FDR	Fund Drive Request	SSA	Search Strategy Advice
FLOCK	Flow Cytometry Analysis Component	SSO	Sequence Specific Oligonucleotides
Fst	Fixation Index	SSP	Sequence Specific Primers
GETS	Government Emergency Telecommunications Service	SSOP	Sequence Specific Oligonucleotide Probes
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	STAR®	Search, Tracking and Registry
GIS	Geographic Information System	TC	Transplant Center
GvHD	Graft vs Host Disease	TED	Transplant Essential Data
HCS	HealthCare Standard	TNC	Total Nucleated Cell
HCT	Hematopoietic Cell Transplantation	TSA	Transportation Security Agency
HEPP	Hospital Emergency Preparedness Program	UI	User Interface
HHQ	Health History Questionnaire	UML	Unified Modeling Language
HHS	Health and Human Services	URD	Unrelated Donor
HIPAA	Health Insurance Portability and Accountability Act	WGA	Whole Genome Amplification
HIS	Hispanic	WMDA	World Marrow Donor Association
HLA	Human Leukocyte Antigen	WU	Work-up
HML	Histoimmunogenetics Mark-up Language		